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THE ASSOCIATION BETWEEN LIVER CIRRHOSIS SEVERITY AND ANEMIA

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Abstract. The etiology of anemia in liver disease is diverse and often multifactorial. Anemia is more severe in advanced stages of liver cirrhosis and can be a predictor of the severity of liver disease.

Methods. In this cross-sectional observational study, we included 181 cirrhotic patients with anemia owing to liver cirrhosis and its complications. The population was divided into 2 groups based on the model for end-stage liver disease (MELD) score and the severity of anemia was assessed in the 2 groups. Similarly, hemoglobin levels were assessed in 3 groups based on the Child-Turcotte-Pugh (CTP) classification.

Results. There was a statistically significant correlation between CTP class and hemoglobin ($P < 0.001$), with the lowest hemoglobin levels in CTP C patients. The correlation coefficient between hemoglobin and MELD score was -0.671 and was statistically significant, establishing that hemoglobin levels decrease with increasing severity of liver cirrhosis. Of 58 patients with macrocytosis, 45 (77.6%) had a MELD score of >12 , whereas only 13 patients (22.4%) had a MELD score of <12 . This difference was statistically significant ($P < 0.0001$).

Conclusions. This study shows that hemoglobin levels decrease with increasing severity of liver disease; thus, this measure can be used in the initial assessment of patients to give a picture of the severity of the disease. A larger prospective trial is needed to establish the use of hemoglobin levels for assessing severity and predicting mortality in patients with liver cirrhosis.

Keywords: Anemia, liver cirrhosis, model for end-stage liver disease score, macrocytosis, Child-Turcotte-Pugh class Introduction

Introduction. Anemia is the most common complication of liver cirrhosis and is seen in 75% of cases [1]. The etiology of anemia in liver disease is diverse and often multifactorial. Common causes include acute and chronic blood loss due to upper gastrointestinal (GI) bleeding, malnutrition, hypersplenism secondary to portal hypertension, and impaired coagulation [2,3]. Alcohol causes anemia by its direct bone marrow toxicity, vitamin B12 and folate deficiency due to poor oral intake, and intestinal malabsorption. Treatment-related anemia is seen in patients with chronic hepatitis C virus infection receiving ribavirin and

interferon. Hepatitis-associated aplastic anemia, characterized by pancytopenia and hypocellular bone marrow, is an entity seen concurrently with or within 6 months of infection with hepatotropic viruses such as hepatitis B, hepatitis C and Epstein–Barr virus [4]. Given the diverse and sometimes multifactorial etiology (alcohol and hepatitis B) of cirrhosis, it is difficult to determine the exact cause of anemia in these groups of patients.

The most common type of anemia encountered in liver cirrhosis is normocytic normochromic anemia, attributable to the chronic inflammatory state [5]. Acute and chronic blood loss from varices, portal hypertensive gastropathy and gastric antral vascular ectasia can give rise to iron-deficiency anemia, in which the picture is one of microcytic hypochromic anemia [6]. Another common hematological abnormality seen in liver cirrhosis is macrocytosis. The causes of macrocytosis in liver cirrhosis are also multifactorial. Vitamin B12 and folate deficiency is also frequently seen in liver cirrhosis, particularly of alcoholic origin, due to malnutrition and intestinal malabsorption. However, liver cirrhosis is characteristically associated with round macrocytes [7-9], whereas B12 and folate deficiency show oval macrocytes and hyper-segmented neutrophils on peripheral blood smear (PBS), along with megaloblastic erythropoiesis on bone marrow examination.

The model for end-stage liver disease (MELD) score was designed to assess the prognosis of cirrhotic patients undergoing trans jugular intrahepatic portosystemic shunt [10]. Three variables—bilirubin, creatinine and international normalized ratio (INR)—each of which has an independent impact on survival, are included in the determination of the MELD score. The MELD score has been adopted since 2002 for organ allocation to patients listed for liver transplantation [11]. Lower hemoglobin (Hb) levels are associated with higher MELD scores and a poor prognosis [12].

This study was carried out to assess the prevalence of various types of anemia in cirrhotic patients and the distribution of the types of anemia in these patients. It also aimed to establish an association between anemia and the severity of liver disease, which could help us to assess our patients better and improve their management.

Methods. This was a cross-sectional observational study carried out at a tertiary care hospital in Western India. The primary objective was to establish an association

between the severity of liver cirrhosis, defined by the MELD score and Hb levels; secondary objectives were to examine the prevalence of various patterns of anemia in liver cirrhosis and assess the relation between macrocytosis and the severity of liver cirrhosis. A total of 181 patients admitted with a diagnosis of liver cirrhosis from January 2019 to April 2019 were enrolled in this study. Ethical clearance was obtained from the institutional ethics committee and all the participants gave written informed consent.

Inclusion criteria were: age >18 years; liver cirrhosis, irrespective of etiology; and Hb <13 g/dL in males and <12 g/dL in females.

Exclusion criteria were: patients who received blood transfusion in the past 3 months; those already on therapy for anemia; presence of chronic kidney disease; and any other etiology of anemia not attributable directly or indirectly to liver cirrhosis.

Liver cirrhosis was defined on the basis of clinical and radiological evidence, such as elastography and ultrasound. Complications, such as ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatorenal syndrome and upper GI bleeding, were also documented. Anemia was defined according to the World Health Organization's criteria (Hb <13 g/dL in males and <12 g/dL in females). A total of 181 patients who satisfied the inclusion and exclusion criteria were enrolled in the study.

All patients underwent thorough history taking and physical examination. Investigations included complete blood counts with platelets, mean corpuscle volume (MCV: <80 fL = microcytic anemia, >98 fL = macrocytic anemia), peripheral blood smear for anemia typing, serum iron studies, serum B12 levels, liver function tests, including prothrombin time (INR), abdominal ultrasound, ascitic fluid analysis and upper GI endoscopy. MELD score was calculated using the formula $9.57 \times \log_e(\text{creatinine mg/dL}) + 3.78 \times \log_e(\text{bilirubin mg/dL}) + 11.2 \times \log_e(\text{INR}) + 6.43$, where 6.43 is the constant for liver disease etiology. The Child–Turcotte–Pugh (CTP) score was also calculated for all the patients.

Statistical analysis. All patients were classified into 4 groups according to their anemia typing (microcytic, macrocytic, normocytic and dimorphic anemia). Patients were further subclassified according to their MELD scores (Group A <12 and Group B >12) and CTP class (Child A, B and C). Univariate and multivariate linear regression analyses were used to examine the associations of the MELD score and CTP score with Hb levels and macrocytosis. Variables with a P-value <0.05 in univariate models were then included in the multivariate analyses. A 2-tailed test was

used to calculate the P-value, and the results were considered statistically significant when the P-value was <0.05 .

Results

Among the 181 patients enrolled 168 were males and 13 were females. The mean age was 49.7 years. Alcohol was the most common etiology (166 patients), followed by cryptogenic (12 patients), Budd–Chiari syndrome (2 patients) and hepatitis B (1 patient).

The mean Hb levels in males and females were 10.51 g/dL and 10.48 g/dL, respectively. Macrocytosis (MCV >98 fL) was seen in 58 (32%) patients. On anemia typing, a total of 93 (51.4%) patients had normocytic normochromic anemia, 56 (30.9%) had macrocytic anemia, 29 (16.0%) had microcytic anemia and 3 (1.7%) had dimorphic anemia (Table 1).

Of the patients who had microcytic anemia on PBS, only 1 had iron-deficiency anemia (serum ferritin <16 $\mu\text{g/L}$ in males and <10 $\mu\text{g/L}$ in females). Of the patients who had macrocytic anemia on PBS, 29 had low serum B12 levels (<220 ng/mL).

Of the 58 patients with macrocytosis, 45 (77.6%) had a MELD score of >12 , whereas only 13 (22.4%) had a MELD score of <12 . This difference was statistically significant ($P<0.001$).

Of the 181 patients, 63 were Child class A, 54 were Child B and 64 were Child C. Hb values were highest for Child A, followed by B and then C (Fig. 1). There was a statistically significant correlation between CTP class and Hb ($P<0.001$) (Table 2). The Pearson correlation coefficient between Hb and MELD score was significant ($P<0.001$) (Table 3, Fig. 2). In addition, there was a significant association between MELD score and serum B12 levels ($P=0.02$); only a quarter of the patients with a high MELD score were deficient in Vit B12 (Table 4).

Discussion

In our study, 51.4% of the patients had normocytic normochromic anemia, 30.9% had macrocytic anemia, 16.0% had microcytic anemia and 1.7% had dimorphic anemia. Iron- deficiency anemia, based on MCV and low serum ferritin levels, was seen only in 1 of 29 patients who had microcytic anemia on PBS. However, the interpretation of routine lab parameters such as serum ferritin is extremely difficult in liver cirrhosis, and bone-marrow staining for iron with Prussian blue is required for the confirmation of the diagnosis.

A total of 58 patients had macrocytosis (MCV >98 fL); of these, 56 had

macrocytic anemia on PBS and 2 had dimorphic anemia. The remaining 51.4% of patients had normocytic normochromic anemia, the most common type of anemia encountered in liver cirrhosis, attributable to the chronic inflammatory state. We also found a significant correlation between MELD score and macrocytosis.

In our study there was a significant correlation between the MELD score and Hb levels. Lower Hb levels were associated with a higher MELD score. Similar findings were seen in a study conducted by Scheiner *et al*, where anemic patients showed a higher MELD (12±4 vs. 9±3; P<0.001) [12]. In a study conducted by Jain *et al*, 88 patients with alcoholic liver cirrhosis were divided into 5 groups according to their MELD scores. It was found that hematological abnormalities, such as anemia and leucopenia, were more common in the higher MELD score group [13]. Studies have shown that anemia is a poor prognostic factor in patients with liver cirrhosis, and the severity of anemia increases with the stage of liver disease [14,15].

We also found a statistically significant correlation between CTP class and Hb. Patients with Child C classification had lower Hb levels compared to those with Child A or B.

Table 1 Demographic profile

Demographic details	
Mean age	49.7 yrs.
Male:female ratio	13:1
Etiology	Frequency
Alcohol	166
Cryptogenic	12
Budd–Chiari syndrome	2
Hepatitis B	1
Mean Hb (g/dL)	
Males	10.51
Females	10.48
Mean corpuscular volume (MCV) (fL)	Frequency
Normocytosis (80-98 fL)	111
Microcytosis (<80 fL)	12
Macrocytosis (>98 fL)	58
Mean MCV of study group	90.3fL
Distribution of anemia	
Normocytic normochromic	93 (51.4%)
Macrocytic	56 (50.9%)

Microcytic	29 (16.0%)
Dimorphic	3 (1.7%)
Child–Turcotte–Pugh class	Frequency
A	63
B	54
C	64
MELD score	
Group A (MELD<12)	114
Group B (MELD>12)	67

MELD, model for end-stage liver disease

Figure 2 Marginal means plot of linear regression analysis showing negative correlation between hemoglobin (Hb) levels and model for end-stage liver disease (MELD) score (P<0.001)

Table 2 Association of Child–Turcotte–Pugh (CTP) class with decreased hemoglobin levels

CTP Class	Number of patients	Mean hemoglobin in (g/dL)	Standard deviation	Standard error	P-value (for difference in means using ANOVA)
A	63	11.86	1.29533	0.16320	<0.001
B	54	10.82	1.63154	0.22202	
C	64	8.92	1.15207	0.14401	
Total	181	10.51	1.84250	0.13695	

Macrocytosis and macrocytic anemia are associated with the severity of liver disease. In a study conducted by Yang *et al*, macrocytic anemia was associated with the severity of liver disease in patients with decompensated cirrhosis related to hepatitis B [16]. The MELD score was used to assess the severity of liver disease in this study. In another study conducted by Yoon *et al*, elevated MCV levels were associated with greater liver cancer mortality in men [17].

Of the 58 patients who had macrocytosis, only 29 had low serum B12 levels. Acute and chronic liver disease is associated with higher serum B12 levels, and this has been attributed to the release of vitamin B12 from the liver as a result of hepatocellular necrosis and increased binding of B12 with serum proteins . In addition, higher B12 levels are associated with severe liver disease and prognosis.

In conclusion, in our study we found a significant correlation between the

MELD score and the degree of anemia. A higher MELD score was associated with more severe hematological complications. Whether the correction of anemia in such patients at an early stage will retard the progression of disease is debatable and requires further studies. However, lower Hb levels were definitely associated with more severe forms of liver cirrhosis, as was established by the correlations.

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[Universal IMPACT factor 7](#)

[SJIF 2022: 4.465](#)

Volume 13 Issue 2

MAY-AUG. 2024

June 2023.

13. Patrice Cacoub, MD. Overview of cryoglobulins and cryoglobulinemia, Up To Date, Wolters Kluver, Up date Sept. 14 2022, Review Febr 2023.

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